Moreover, Applicants gratefully acknowledge withdrawal of finality of the previous Office Action dated March 10, 2000.

Claims 1, 2, 4, 7, 8, 14, 67 , 69, 71 and 72 stand rejected as being unpatentable over WO 96/18105 ("Strominger"), in view of U.S. Pat. No. 5,759,817 ("Barbas"), Onda et al. (*Mol. Immunology* 32: 1387 (1995) "Onda"), and Huse et al. (*Immunol.* 149: 3914, (1992); "Huse").

In formulating the rejection it was alleged that Applicant's Rule 131 Declaration filed on December 27, 1999 did not address the claimed invention ie., fusion protein including a Cβ fragment. Office Action at pg. 5. Applicants respectfully disagree with that assertion.

Before turning to the outstanding rejection, it is noted that the USPTO previously determined that the Rule 131 Declaration addressed the claimed invention comprising a Cβ fragment:

> [t]he Declaration is sufficient to establish that the TCR fusion protein having the structural characteristics of the fusion protein claimed in claims 1, 2, 4, 7-8, 14, 19, 67 and 71-72 was made before June 13, 1996.
>
> Office Action dated March 10, 2000 (Paper No. 22) at pg. 7.

Applicants agree. To address the opposite the position now taken, it is emphasized that the pKC44 vector stated in the Rule 131 Declaration includes the Cβ fragment.

In particular, Applicants stated that the pKC44 vector was made from pKC42 vector which vector has sequence encoding a V-β C-β bacteriophage gene VIII fusion protein.

> Well before Strominger's June 1996 publication date, we inserted sequence encoding the V-beta **C-beta** bacteriophage gene VIII fusion protein into the pKC42 vector. Attached as Exhibit 6 is a true and accurate copy of notes made by one of us, with dates deleted, showing, among other things, production of the pKC44 vector (encodes single-chain fusion protein). In particular, pages 1-5 of the notes show manipulation of specific

pKC42 vectors (42.1, 42.2, and 42.3) and use of those vectors as recipients of sequence encoding the V-beta C-**beta** bacteriophage gene VIII construct.

Rule 131 Declaration at paragraph 13 (emphases added).

The Declaration specifically includes mention of an experimental objective of the data presented " To ligate β [Cβ] + gene VIII into pKC42.3 to yield 2 single chain constructs". See Exhibit 6 at pg. 4 (emphasis added).

Single-chain fusion protein encoded by the pKC44 vector, for example, were made well before Strominger's 1996 publication date. See paragraphs 13-15 of the Declaration.

Accordingly, it is submitted that Applicants' Rule 131 Declaration squarely addresses the claimed invention ie., the fusion protein of claim 1 which includes the Cβ fragment.

It was indicated by Dr. Schwadron during the October 25, 2000 interview that additional information relating to construction of the pKC44 vector and manipulation of its Cβ fragment would be appreciated. In line with this request, Applicants hereby submit a Rule 132 Declaration of Kimberlyn F. Card stating that the pKC44 vector includes the Cβ fragment.

In particular, the Rule 132 Declaration states that the pKC44 vector includes sequence that encodes the Cβ fragment. See paragraphs 4-10, for example.

Appendix 1 of the Rule 132 Declaration summarizes manipulation of parental vectors to make the pKC44 vector encoding the Cβ fragment. See paragraph 10.

In view thereof, it is submitted that Applicants have antedated Strominger's publication date of June 13, 1996. Strominger should be withdrawn as a §103 reference in this case and such action is respectfully requested.

None of the other references cited by the Examiner teach, suggest or provide any motivation to make the molecules reported by Strominger. Reconsideration and withdrawal of the rejection are requested.

Claims 1, 2, 4, 7, 8, 14, 67, 69, 71 and 72 stand rejected as being unpatentable over Chung et al. (PNAS 91: 12654 (1994) in view of U.S. Pat. No. 5,759,817 ("Barbas"), Onda et al. (*Mol. Immunology* 32: 1387 (1995) "Onda"), and Huse et al. (*Immunol.* 149: 3914, (1992); "Huse"). Applicants respectfully disagree with the rejection.

The position taken in the rejection is that it would be obvious to fuse the single-chain TCRs taught by Chung with the bacteriophage coat protein reported by Barbas. Applicants cannot agree.

As relied on, Chung reports TCRs linked to a cell membrane anchor (glycosysl phosphatidylinositol (GPI) or murine CD3 ζ chain). The anchor is taught to help express the single-chain TCRs. See Chung e.g, at pg. 12654 at cols. 1-2. The anchor molecules Chung teaches are different from the coat proteins of Barbas. For example, Chung's molecules are disclosed as cell membrane proteins while those of Barbas are bacteriophage coat components. As understood, the anchor molecules have transmembrane domains that assist in a fluid cell membrane setting. In contrast, Barbas' coat proteins do not have those domains. Further, Chung's molecules are reported to "anchor" proteins to the cell membrane while those of Barbas provide a "coat" function. There is nothing in the cited references that teaches or suggests that Chung's molecules and Barbas' bacteriophage coat proteins are interchangeable particularly with respect to a single chain TCR molecule.

To establish a *prima facie* case, the USPTO must point to some suggestion or motivation to modify the cited references in the way the instant obviousness rejection has done. That burden has not been met here. For example, argument offered at page 7 of the present Office Action falls short of establishing any nexus between Chung's anchor molecules and Barbas' coat proteins. That "Barbas et al. and Onda et al. teach TCR-bacteriophage VII coat fusion proteins.."

is not germane because, as cited, the Barbas' TCRs are heterodimers ie., two chain molecules in which the V chains are on separate chains. They are not the soluble single chain TCR molecules of the invention in which the V chains are present on one chain. See pg. 7 of the Office Action. There is simply no suggestion or motivation in the cited references, taken individually or together, that one could replace Chung's anchoring molecules with Barbas' coat proteins to make Applicants' single chain TCR molecule. See MPEP 706.02(j) (requiring that such a suggestion or motivation be found to substantiate the *prima facie* case).

Moreover, the cited references provide no reasonable expectation that switching Chung's anchoring molecules with the phage coat proteins of Barbas would be successful. Again, that Barbas and Onda, as cited, report limited success about making different TCR constructs (two chain heterodimers) is not enough to support the *prima facie* case. The reasonable expectation required by the patent laws must be found in the cited references and not the instant disclosure. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

It is submitted that the instant *prima facie* case of obviousness cannot withstand scrutiny. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants disagree with the rejection on other grounds.

For example, it is well-established patent law that that evidence of secondary considerations such as long-felt need and failure of others is an indicia of non-obviousness. This is sometimes referred to as the fourth factual inquiry enunciated by the U.S. Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). The USPTO is duty bound to consider such evidence. See MPEP 2141.

In the instant case, there has been long-felt need and failure in the field of the invention notwithstanding the obviousness position taken in the present Office Action.

For example, in a recent peer-reviewed article by Holler et al., the authors report that phage display with single chain TCRs has not yet been successful. The phage display related by Holler involves presenting single-chain TCR molecules fused to a bacteriophage coat protein.

Phage display (cite omitted) **has not yet proven successful in the engineering of single-chain TCRs (scTCRs, Vβ-linker-α) despite extensive structural similarity between antibody and TCR V regions.**

Holler et al. (2000) in *Proceedings of the National Academy of Sciences*, 97: 5387 at 5389, col. 2 (copy enclosed).

Holler provides objective evidence that workers in the field have tried, but failed to make and use single chain TCR proteins with fused phage protein. Applicants' invention addresses this long-felt need by providing soluble fusion molecules with a bacteriophage coat protein linked to a single chain TCR. That is, Applicants have succeeded in making and using such molecules in the face of failure by others. The Holler reference is highly probative of the difficulties experienced in the field and should be given "substantial weight" by the Examiner in his consideration of the outstanding obviousness rejection. See MPEP 716.01(b).

Applicants disagree with the rejection on other grounds.

For example, the instant rejection relies on Onda as follows:

> Onda et al. disclose a soluble fusion protein comprising a bacteriophage coat protein covalently linked to a **single-chain T cell receptor** by a peptide linker sequence wherein the single TCR china is the alpha chain and the bacteriophage coat protein is cpVII (see abstract and Figure 1, in particular). Onda et al. also teach that TCR-bacteriophage coat protein fusion protein can be used to study specific binding interactions of the TCR chain to antigenic ligands (see paragraph bridging pages 1394-1395, in particular).

Office Action at 6-7 (emphasis added).

Respectfully, this reading of Onda is incorrect and at odds with what the reference fairly teaches.

For example, the rejection takes the position that Onda discloses making single-chain T-cell receptor. Respectfully, this is not correct. As understood, **Onda does not disclose fusion of a single-chain T-cell receptor** to a bacteriophage fusion protein. Instead, Onda reports fusing a small TCR fragment (V-α chain) to a bacteriophage coat protein.

> We utilized an M13 phage display system, designed for multivalent receptor display, to explore specific binding interactions between various TCR α **chains** and specific antigen in the absence of MHC.
>
> Onda's Abstract at pg. 1387 (emphasis added).

Onda's fusion proteins are completely different from those claimed by Applicants. Particularly, the V-α chain of Onda's fusion proteins are substantially smaller than the single-chain T-cell receptor (includes V-α + V-β chains) that Applicants have successfully manipulated. Accordingly, Onda, as relied on, is not the Applicants' invention.

The cited portions of Onda simply do not teach, suggest or provide any motivation to fuse a single-chain TCR (V-α and V-β chain) and a bacteriophage coat protein as alleged in the rejection. As cited, none of the other references make up for this deficiency. Reconsideration and withdrawal of the obviousness rejection are therefore requested.

Applicants respectfully disagree with the rejection on other still further grounds.

For example, the position taken in the rejection is that Onda teaches that a TCR-bacteriophage fusion protein can be used to study TCRs. Respectfully, Onda does not teach this. Instead, the reference reports that fusion molecules having a small part of a TCR (V-α chain) have **unusual uses that are not characteristic of TCRs**.

> Our results extend these findings by demonstrating that the dominant interactions of certain **TCRα chains** for peptide antigens may be sufficiently high that they can be

> analysed independently. However, these interactions are **quite unusual** in that they do not require the expression of the second TCR subunit or normal MHC and coreceptor interactions. **These results may raise concern that this model does not reflect typical TCR-ligand interactions.**
>
> Onda at page 1395, col. 1 (emphases added).

Put another way, Onda's fusion molecules are taught to bind antigen even without help from the TCR V-β chain. Clearly, there is nothing in this observation, taken by itself or with the other cited references, that teaches, suggests or provides any motivation to change Onda's antigen binding molecules by adding a V-β chain. At least in Onda's hands, antigen binding can be achieved without the V-β chain that is specifically included in Applicants' claimed invention (see claim 1, for example).

> Significantly, only some of Onda's Vα chain fusion proteins are reported to bind antigen.
>
> ...**only a subset of TCR Vα have capacity for direct interactions with antigen strong enough to be detectable in this system.**
>
> Onda at page 1395, col. 2, second full paragraph (emphasis added).

Thus **according to Onda some V-α chain bacteriophage fusion proteins work and some do not**. In view of this warning, it is not seen how one would know that it is possible to fuse a larger V-α V-β chain to bacteriophage coat protein and achieve good antigen binding.

Of those V-α chain bacteriophage fusion molecules that Onda did get to work, and these are not many, the reference describes them as exemplifying **unusual TCR interactions**. Thus, Onda does not provide any motivation to make larger, and perhaps more unusual, V-α V-β fusion molecules to analyze antigen binding interactions.

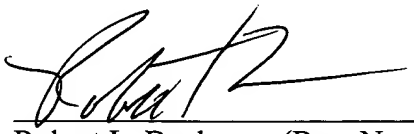
Fairly read, Onda does not teach, suggest or provide any motivation to fuse a single-chain TCR (V-α and V-β chain) to a bacteriophage coat protein as Applicants have done. None of the cited references remedy this defect.

Additionally, **Onda teaches** away from the present invention by disclosing that at least in their hands **many V-α chain fusion proteins do not bind antigen**. In marked contrast, Applicants have found that such fusions bind antigen particularly in the context of the V-α Vβ chain bacteriophage coat protein fusions of this invention. Reconsideration and withdrawal of the rejection are requested.

As mentioned in the prior Response, the office action dated June 23, 1998 indicated that PTO Form 948 (Notice of Draftsperson's Patent Drawing Review) was attached thereto. Applicants' representative has not received the PTO Form 948. The undersigned would be most grateful if the Examiner could forward that form in due course.

Although it is not believed that any fee is needed to consider this submission, the Examiner is authorized to charge our deposit account no. 04-1105 should any fee be needed.

Respectfully submitted,



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Date: February 21, 2001

Doc. 143111